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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,422	03/23/2004	Teiji Ekida	Q-80657	2829

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EXAMINER	
MERTZ, PREMA MARIA	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/806,422	EKIDA ET AL.	
	Examiner	Art Unit	
	Prema M. Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *3-12 and 18-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1-2, 17) in the reply filed on 2/28/06 is acknowledged.

Claim 3-12, 17 are withdrawn from further consideration by the examiner, as being drawn to a non-elected invention.

Information Disclosure Statement

2. Applicant's IDS submitted on 3/23/04 is acknowledged and has been fully considered. A signed copy is attached hereto.

Claim Rejections - 35 USC § 112, first paragraph, scope of enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3a. Claims 1, 2, and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) an IL-6 receptor-IL-6 fusion protein, comprising the IL-6 receptor (IL-6R) of amino acid sequence set forth in SEQ ID NO:63 at the N-terminus of said fusion protein directly linked to IL-6 of amino acid sequence set forth in SEQ ID NO:64 at the C-terminus of said fusion protein, wherein said fusion protein forms an oligomeric complex with gp130 and wherein said fusion protein induces go130 activation; does not reasonably provide enablement for a fusion protein comprising a fragment of the IL-6 receptor (SEQ ID NO:63) directly linked to a fragment of IL-6 of amino acid sequence set forth in SEQ ID NO:64

or a fusion protein as recited in claim 2 which encompasses a fusion protein comprising any of amino acids 1 to 116 through any of amino acids 323 to 468 of the IL-6 receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1 recites a fusion protein, which encompasses a fusion protein in which any one amino acid from the IL-6 receptor (SEQ ID NO:63) is directly linked to any one amino acid residue from IL-6 (SEQ ID NO:64), which claims are overly broad, since no guidance is provided as to which of the myriad of fusion protein molecules encompassed by the claims will retain the characteristics of the desired fusion polypeptide (made protease-resistant to the protease secreted by the host cell, page 12, last para). Variants of the protein or nucleic acid molecule can be generated by insertions, deletions or substitutions of amino acids or nucleotides respectively (page 12, first full para). However, Applicants have failed to disclose actual or prophetic examples on expected performance parameters for all of the possible claimed fusion protein molecules. Moreover, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Mikayama et al. (1993) teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution

in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

Cytokine fusion proteins are well known in the art. Additionally, IL-6, IL-6R fusion proteins are well known in the art. The instant claims recite a fusion protein comprising a fragment of IL-6 and a fragment of IL-6R. Other than the fusion proteins recited on pages 8-11, the instant specification does not teach fragments of IL-6 or IL-6R that may be directly linked to form an oligomeric complex with gp130, and wherein said fusion protein induces gp130 activation. There is no guidance provided in the specification as to how one of ordinary skill in the art would generate a fusion protein other than that exemplified in the specification (pages 8-11). See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Given the breadth of the claims, in light of the predictability of the art as determined by the number of working

examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention. The guidance provided in the specification is not commensurate with the full scope of the claims.

Claim Rejections - 35 USC § 112, second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 17, are indefinite in the recitation of the term "a fragment". This language is vague and indefinite since it encompasses potentially any portion of the polypeptide including a single amino acid. There is no guidance provided as to what specific sequences the term "fragment" refers to. Therefore, the metes and bounds of the claims are unclear.

Claim rejections-35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5a. Claims 1-2, 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fischer et al (1997).

Fischer et al. disclose a human IL-6 receptor.IL-6 fusion protein comprising the soluble IL-6 receptor (sIL-6R corresponding to amino acids 113-323) fused to IL-6 (corresponding to amino acid residues 29-212) by a flexible peptide linker (see abstract; Figure 1; page 145, column 1). However, Fischer et al never obtained a fusion protein of sIL-6R and IL-6 without the linker.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant invention was made to remove the linker between the sIL-6R and IL-6 altogether and link the proteins directly. To remove the linker altogether would have been *prima facie* obvious to one in the art of molecular biology at the time that the instant invention was made relative to its art intended use because in the development of a fusion protein as a medicine, it is desirable to minimize immune reaction problems.

Conclusion

No claim is allowed.

Claims 1-2, 17 are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Prema Mertz

Prema Mertz Ph.D., J.D.
Primary Examiner
Art Unit 1646
April 4, 2006